**AUS DEM LEHRSTUHL FÜR**
**PSYCHIATRIE UND PSYCHOTHERAPIE**
**ÄRZTLICHER DIREKTOR: PROF. DR. MED. HELMFRIED E. KLEIN**
**DER MEDIZINISCHEN FAKULTÄT**
**DER UNIVERSITÄT REGENSBURG**

**Thema:**

# Arzneimittelinteraktionen über das humane hepatische Phase-II-Enzym UDP-Glucuronosyltransferase (UGT)

Inaugural - Dissertation
zur Erlangung des Doktorgrades
der Zahnmedizin

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Medizinischen Fakultät
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# Inhalt

# 1. Einleitung

## 1.1. Grundlagen der Enzymgenetik

### a) Enzyme

Enzyme sind Proteine, die in der Funktion als Biokatalysatoren die Reaktionsgeschwindigkeit biochemischer Reaktionen ubiquitär in allen Organismen um ein Vielfaches (um bis zu einem Faktor von $10^{28}$) erhöhen. Dabei geht das Enzym für kurze Zeit eine Verbindung mit den Reaktionspartnern, den Substraten ein. Es gibt sechs Klassen von Proteinen, deren Nomenklatur sich von den durch sie katalysierten Reaktionen ableitet: Oxidoreduktasen, Transferasen, Hydrolasen, Lyasen, Isomerasen und Ligasen. Enzyme besitzen ein sogenanntes aktives Zentrum, durch das die Reaktionspartner miteinander in Kontakt treten, und so einen Enzym-Substrat-Komplex bilden. Der Substratumsatz pro Zeiteinheit, d. h. die Reaktionsgeschwindigkeit, dient als Maß für die Enzymaktivität. Eine Regulation der Enzymaktivitäten im Körper findet über sogenannte allosterische Effektoren (Inhibitoren, Aktivatoren) statt. Diese binden covalent an einer Stelle des Enzyms außerhalb des aktiven Zentrums und bewirken so eine Konformitätsänderung, die zu einer reversiblen oder irreversiblen Änderung der Enzymaktivität führt[1].

### b) Polymorphismen

Der Einfluss von sogenannten genetischen Polymorphismen auf die Aktiviät von Enzymen, die im Arzneistoffwechsel aktiv sind, wie zum Beispiel die unter anderem in der Leber vorkommenden Glucuronosyltransferasen ist Gegenstand einer Vielzahl von Untersuchungen. Man spricht in diesem Zusammenhang von einem aus dem Bereich der Pflanzenwelt übernommenen Begriff, dem sogenannten Wildtyp, d. h. die in der freien Natur am häufigsten vorkommenden Erscheinungsform. Der Begriff bezieht sich sowohl auf den Organismus als auch auf einzelne Gene. Abweichungen eines Wildtyps sind Mutationen, deren Auftreten eine

Vielzahl an Ursachen hat. Man unterscheidet grundsätzlich zwischen Chromosomen- und Punktmutationen. Bei Mutationen können ganze Chromosomen fehlen, oder auch zusätzlich auftreten. Ein bekanntes Beispiel ist die Trisomie 21 mit drei, statt zwei 18X Chromosomen. Bei den Punktmutationen können entweder ganze Bruchstücke, oder nur einzelne Basenpaare aus einer Gensequenz ausgetauscht, oder gelöscht sein (Deletion), oder zusätzlich auftreten. Die Ursachen können beispielsweise in einer fehlerhaften Replikation des Gens liegen, spontan auftreten, erblich bedingt sein, oder auch durch äußere Einflüsse hervorgerufen werden. Im Rahmen der Mutationen sind die sogenannten Polymorphismen zu etwa 90 % für interindividuelle genetische Unterschiede verantwortlich.[2]

Als Polymorphismen bezeichnet man genetische Sequenzunterschiede, die im Vergleich zum „normalen“ Gen, also dem Wildtyp, mit einer Häufigkeit von mindestens 1% auftreten. Polymorphismen können bei allen Genen auftreten.

Genetische Polymorphismen an Enzymen, die für den Metabolismus von Arzneimitteln entscheidend sind, können die Enzymaktivität deutlich verändern. So resultieren für bestimmte Enzymvarianten langsame, schnelle und normale Metabolisierer. Ein wichtiger genetischer Polymorphismus betrifft zum Beispiel Arzneistoffe wie Antiarrythmika, Antidepressiva oder Codein, die über das sehr gut untersuchte CYP 2D6 metabolisiert werden. Eine genetische Untersuchung wäre demnach beispielsweise sinnvoll für Patienten, die mit Arzneistoffen mit einer sehr geringen therapeutischen Breite therapiert werden[3].

Die unterschiedliche Aktivität bei Patienten mit verschiedenen Isoformen dieses Enzyms führt zu Diskrepanzen zwischen Verträglichkeit und Wirksamkeit von Arzneimitteln. Substrate dieses Enzyms sind z.B. Betablocker und Antidepressiva. Eingeteilt werden die verschiedenen Phänotypen der Metabolisierer in so genannte poor-, extensive- und ultra extensive metabolizer, je nachdem wie schnell bzw. langsam sich die Plasmakonzentration eines Arzneistoffes nach Einnahme verändert.[4] 5-10% der Patienten sind hierbei schwache, 1-10% ultraschnelle Metabolisierer. Genetische Polymorphismen können ebenso die

pharmakodynamische Wirkung eines Arzneistoffes verändern, indem sie nicht den Arzneimittelmetabolismus, aber den biologischen Effekt dieses Arzneistoffes verändern. Das Antipsychiotikum Sertindol beispielsweise kann als Nebenwirkung die QT- Zeit im EKG verlängern. [5]

### 1.2. Bedeutung der Arzneimittelinteraktionen in Deutschland

Mögliche Wechselwirkungen von Arzneimitteln spielen eine entscheidende Rolle in der Auswahl des richtigen Medikamentes, vor allem im Rahmen von Kombinationstherapien. Einflussfaktoren sind nicht nur die Metabolisierungswege, sondern auch das Alter, das Geschlecht, oder das Bestehen von anderen Krankheiten wie Leber- oder Niereninsuffizienz. Unerwünschte Arzneimittelwirkungen, kurz UAW, treten bei etwa 5% der Patienten auf. Man fand heraus, dass bei etwa 3-6% der stationären Aufnahmen in Deutschland diese die Ursachen für die Aufnahme sind und sogar für 0,15% der Todesfälle in den Kliniken verantwortlich sind, wobei knapp die Hälfte davon mit einer nicht korrekten Anwendung des Medikamentes, d.h. also beispielsweise mit Incompliance bzw. mit Behandlungsfehlern im Zusammenhang steht[6]. Unter Incompliance versteht man beispielsweise eine nicht korrekte Einnahme der verordneten Dosis durch den Patienten, oder die Einnahme zum falschen Zeitpunkt, bzw. das nicht Einnehmen der Medikamente. Die Bandbreite von Nebenwirkungen unter Arzneimitteltherapie reicht von vergleichsweise harmlosen und häufigen Erscheinungen wie Müdigkeit oder leichter Übelkeit bis zu schweren Nebenwirkungen wie durch Therapie von schwangeren Frauen mit dem damals als unbedenklich geltenden schlaffördernden Mittel Contergan® (Thalidomid) in den 60er Jahren[7]. Das Medikament führte nach Einnahme durch Schwangere zu Behinderungen des Neugeborenen (Amelie), sodass es schließlich vom Markt genommen werden musste.

### 1.3. Elimination und Metabolismus von Arzneimitteln

Arzneimittelabbau bezeichnet die Metabolisierung, biochemische Modifikation von Stoffen z.B. mittels spezieller enzymatischer Systeme und deren Elimination. Bei der Verstoffwechselung von Arzneimitteln werden beispielsweise lipophile chemische Komponenten in besser vom Körper ausscheidbare hydrophile Substanzen umgewandelt. Die Geschwindigkeit dieses Umwandlungsvorganges spielt eine wichtige Rolle für die Verweildauer im menschlichen Körper und die Intensität der pharmakologischen Wirkung des Arzneistoffes. Ammoniak beispielsweise, eine bei dem Abbau von bestimmten Aminosäuren anfallende starke Base, muss im Körper einen speziellen Eliminierungsprozess durchlaufen, da es als NH3 und NH4+ in höheren Konzentrationen toxisch ist und vor allem das Gehirn schädigen kann. Ammoniak wird in der Leber im sogenannten Harnstoff-Zyklus abgebaut. Es entsteht Harnstoff in einer zyklischen Folge von Reaktionen, die in den Mitochondrien, bzw. im Cytoplasma stattfinden. Der Harnstoff wird anschließend über die Nieren ausgeschieden[8]. Meistens äußert sich dieser Prozess der Umwandlung also in einer Detoxifikation (Umwandlung in eine für den Körper nicht toxische, ausscheidbare Substanz) des entsprechenden Medikamentes. Arzneimittel stellen fast ausschließlich Xenobiotika (vom Körper aufgenommene Fremdstoffe natürlichen Ursprungs, d. h. nicht vom Menschen künstlich erzeugt) dar, wobei aber auch organische Chemikalien mit Hilfe derselben enzymatischen Systeme verstoffwechselt werden. Hier ergeben sich zahlreiche mögliche Interaktionen verschiedener Medikamente, bzw. Interaktionen des Arzneimittels und anderer Stoffe.

Der Prozess der Metabolisierung der meisten Medikamente findet hauptsächlich in der Leber statt und wird aufgeteilt in zwei Phasen. Unter der Phase I, die oft, jedoch nicht zwingend der zweiten vorausgeht, versteht man alle Stoffwechselprozesse, die mit einer Veränderung des Wirkstoffmoleküls verbunden sind. Sie umschließt die hydrolytische Spaltung, Oxidation, Reduktion, Alkylierung und Desalkylierung. Bei den Reaktionen der Phase II entstehen

sogenannte Kopplungsprodukte aus dem Arzneistoff selbst oder einem seiner in Phase I gebildeten Metaboliten. Die wichtigsten Kopplungsreaktionen des Phase II Stoffwechsels sind die Glucuronidation, Sulfatisierung, Acetylierung, Methylierung, Glycinierung und Kopplung an Gluthation. Ein Beispiel für das letztgenannte ist die Metabolisierung von Paracetamol. Das antipyretisch wirkende Analgetikum wird nach Kopplung mit Schwefel- und Glucuronsäure über die Nieren eliminiert, mit einer Eliminationshalbwertszeit von zwei Stunden. Jedoch wird Paracetamol zum Teil auch über die Leber mittels des Enzymsystems Cytochrom-P-450 in einen reaktiven Metaboliten umgewandelt, N-Acetyl-p-benzochinonimin (NAPQI), das durch Kopplung an Glutathion, einem Tripeptid aus den drei Aminosäuren Glutamat, Cystein und Glycin, entgiftet wird[9]. Bei eventueller Intoxikation durch Paracetamol droht ein absolutes Leberversagen durch Erschöpfung der Gluthationreserven. Statt an das unschädliche Glutathion bindet der Metabolit nun an Proteine der Leberzellen, woraufhin diese absterben.[10] Diesem kann durch Gabe von N-Acetylcystein entgegnet werden.

Unter Glucuronidation versteht man den Prozess der chemischen Bindung einer Substanz an Glucuronsäure mittels einer glycosidischen Bindung. Das resultierende Glucuronid ist typischerweise viel wasserlöslicher als das Ausgangsprodukt. Der menschliche Körper verwendet die Glucuronidation für die Ausscheidung von körpereigenen Stoffen wie Bilirubin, Östrogene oder Mineralkortikoide[11].

Die daran beteiligten Enzyme befinden sich hauptsächlich in der Leber und heißen Uridindiphosphatglucuronosyltransferasen (UDP- Glucuronosyltransferasen).

### 1.4. Pharmakovigilanz + therapeutisches Drug Monitoring

Die Arzneimittelwirkung wird unter anderem bestimmt von der Pharmakodynamik (Wirkung des Medikamentes am Zielort) und der Pharmakokinetik (individuelle Metabolisierung und Elimination).

Aufgrund der großen individuellen pharmakokinetischen Unterschiede stellt sich die Frage, ob eine allgemeine Genotypisierung sinnvoll wäre. Hier würden die für den Arzneimittelmetabolismus entscheidenden genetischen Abschnitte untersucht und ermittelt, ob eine beschleunigte oder verlangsamte Verstoffwechselung über die betreffenden Enzyme zu erwarten ist. Somit ließe sich erreichen, dass die Dosierung verabreichter pharmakologischer Substanzen individuell besser angepasst werden kann, um somit unerwünschte Nebenwirkungen zu vermeiden. Die Genotypisierung ist allerdings noch nicht als Routineverfahren etabliert, auch aus ökonomischen Gesichtspunkten. Selbst bei routinemäßiger Analyse des genetischen Materials vor Arzneimitteltherapie bliebe das Problem der Wechselwirkungen der Arzneimittel untereinander oder einer Incompliance nicht berücksichtigt[12].

Eine wichtige Möglichkeit der Qualitätssicherung der Arzneimitteltherapie stellt das Therapeutische Drug Monitoring (TDM) dar. Hier werden Konzentrationen von Arzneistoffen im Blut der Patienten regelmäßig gemessen, um beispielsweise bei Medikamenten mit einer geringen therapeutischen Breite dosisabhängige UAW zu vermeiden. Das TDM, d.h. Messungen der Plasmakonzentration von pharmakologischen Substanzen, die auf einen Zusammenhang zwischen Plasmakonzentration und klinischer Wirkung schließen lassen ist bereits für Arzneimittel wie z. B. Lithiumsalze etabliert und empfohlen.

Um die Therapie speziell mit Psychopharmaka noch weiter zu verbessern, hat die Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychatrie (AGNP) Konsensusleitlinien für das Therapeutische Drug Monitoring (TDM) entwickelt.

Die Leitlinien enthalten unter anderem Empfehlungsgrade für die Durchführung des TDM für die meisten Psychopharmaka. Das Therapeutische Drug-Monitoring birgt Fehlerquellen in sich. Ein Problem wäre beispielsweise schlecht etablierte Referenzbereiche, was vor allem bei Medikamenten mit geringer therapeutischer Breite riskant wäre. Ebenfalls stellt der Zeitpunkt der Blutabnahme eine potentielle Fehlerquelle dar, da nicht immer gewährleistet ist, dass die

Blutabnahme vor der nächsten Medikamenteneinnahme (Talspiegel) erfolgt. Eine Fehlbeurteilung würde sich ergeben, wenn bei einem Patienten anstatt eines schnellen Metabolisierers beispielsweise fälschlicherweise die Diagnose der Incompliance gestellt würde. (Noch unbekannte) Arzneimittelinteraktionen könnten die Ergebnisse ebenfalls verfälschen, bzw. ungeklärte Fragen hinterlassen.

Durch die Einführung des TDM konnte die Arzneimittelsicherheit entscheidend verbessert werden[13]. Die Pharmakovigilanz, d.h. die systematische Überwachung der Sicherheit eines Arzneimittels vor allem nach Markteinführung ist ein weiterer wichtiger Bestandteil der Arzneimittelsicherheit. Nach dem Thalidomid-Skandal wurde in Deutschland 1968 die Meldung von UAW in die ärztliche Berufsordnung verankert. Derzeit gibt es bereits einige Arbeitsgemeinschaften, die als Spontanerfassungssystem UAW sammeln und an die nationalen Meldestellen weiterleiten (z. B. in der Psychiatrie: AGATE (Arbeitsgemeinschaft Arzneimitteltherapie bei psychiatrischen Erkrankungen) und AMSP (Institut für Arzneimittelsicherheit in der Psychiatrie e.V.). Die Weltgesundheitsorganisation WHO definiert die Pharmakovigilanz folgendermaßen: Wissenschaft und alle Aktivitäten, die sich mit der Aufdeckung, Bewertung, dem Verstehen und der Prävention von Nebenwirkungen oder von anderen Arzneimittel-bezogenen Problemen befassen.

- Analyse und Abwehr von Arzneimittelrisiken
- Aktivitäten, die zur Entdeckung, Beurteilung sowie zum Verständnis und zur Vorbeugung von unerwünschten Wirkungen oder anderen Problemen in Verbindung mit Arzneimitteln dienen
- Vorbeugung von Therapiefehlern, Vermittlung von Arzneimittelinformationen
- Förderung der rationalen Therapie mit Arzneimitteln[14]

## 1.5. UGTs

### a) Aufbau

Die Superfamilie der UGT ist beteiligt am Abbau von Arzneistoffen, Steroidhormonen, und Schadstoffen, die der Körper durch sie in eine biologisch inaktive, ausscheidbare Form überführt. Hierzu übertragen die Enzyme Glucuronsäure an funktionelle Gruppen lipophiler Verbindungen, wie etwa Hydroxy-, Carboxy-, Amino-, und SH- Gruppen. Im menschlichen Körper sind die UGT-Enzyme bei der Entgiftung und Elimination von Schadstoffen beteiligt. Substrate sind hauptsächlich Bilirubin, Gallensäuren, Umweltgifte und Medikamente.

Die UGTs befinden sich hauptsächlich in der Leber, ließen sich aber auch in anderen Regionen, unter anderem im Gehirn nachweisen. Außerdem findet man sie noch in Darm, Nieren, Lunge, Prostata und Haut. Lokalisiert sind sie im endoplasmatischen Retikulum der Zellen. Eine Nomenklatur dieser Enzyme wurde im Jahre 1997 eingeführt[15]. Derzeit sind über 35 verschiedene UGTs bekannt. Die Nomenklatursystematik wurde ähnlich der des Cytochrom P 450 erstellt. Die erste Zahl steht für die Genfamilie, z.B. die 1 bei UGT1A4, der Buchstabe A für die Subfamilie und die anschließende Zahl 4 für das individuelle Gen, bzw. das Isoenzym. Sie werden eingeteilt in die Gruppe der UGT1, und UGT2 Genfamilie. Während die UGT1 Gruppe hauptsächlich am Abbau von Substraten aus der Gruppe der Bilirubine, Amine und Phenole beteiligt ist, bauen die UGT2 vor allem Substrate der Gruppe der Steroide und Opioide ab[16]. Mutationen des UGT1A1 sind verantwortlich für Krankheiten wie dem Morbus Meulengracht oder das Crijgler- Naijar Syndrom, bei dem es durch die Bilirubinenzephalopathie sogar zum Tod des Säuglings kommen kann[17]. Bei Morbus Meulengracht kommt es zu einer 70 – 75 %igen Reduktion der Enzymaktivität bei einer Mutation des UGT1A4 Enzyms, zu 50 % bei UGT1A6, und 83 % bei UGT1A7. Bei einem Rückgang auf 0 bis 10 % spricht man vom Krankheitsbild des Crijgler- Naijar. Das UGT1A1 sorgt normalerweise im Prozess des Hämoglobinabbaus durch Glukuronsäure zur Überführung der wasserunlöslichen, in die wasserlösliche Form des Bilirubins. Bei einem

Rückgang der Aktivität ist nun die Bildung des konjugierten, und damit wasserlöslichen Bilirubins erschwert, sodass es zu einem erhöhten Bilirubinserumspiegel kommt. Das für UGT1A1 codierende Enzym besitzt im Normalfall eine Promotor TATA Box (eine DNA Sequenz in der Promotorregion eines Gens zur Regulierung der Transkription) mit den Allelen A(TA6)TAA, während bei der Krankheit ein homozygotes Allel A(TA7)TAA vorliegt. Den Polymorphismus dieser Mutation nennt man UGT1A1*28[18]. Als Allel bezeichnet man die für ein Merkmal verantwortlichen Faktoren oder Gene, die in zwei sich ausschließenden Formen vorkommen. Jedes der beiden Allele stammt von einem Elternteil[19]. Man geht davon aus, dass das Wissen über die UGT Enzyme derzeit auf dem Stand ist, auf dem das Wissen über die allgemein bekannteren P450 Cytochrome vor 10 Jahren war[20].

**b) Aufgaben**

Die Aufgaben der UGTs werden anhand zweier Beispiele im Folgenden erläutert:

1. Das nonsteroidale Antiöstrogen Tamoxifen wurde erstmals 1977 eingesetzt für die Prävention und Behandlung von Brustkrebs. Auffallend war bei der Behandlung die interindividuelle Reaktion der verschiedenen Patienten auf dieses Medikament, sowie diverse Nebenwirkungen wie tiefe Beinvenenthrombosen oder die Entstehung von Dünndarmkrebs. Man versuchte herauszufinden, wodurch diese unterschiedlichen Reaktionen auf ein und dasselbe Medikament begründet waren. Die verschiedenen Wege der Metabolisierung von Tamoxifen wurden daraufhin näher untersucht. Neben der Metabolisierung durch Cytochrom P 450, kurz CYP450, fand man heraus, dass die Familie der UGT-Enzyme wesentlich bei dem Abbau von Tamoxifen beteiligt ist, das UGT1A4 am hauptsächlichsten. Beteiligt sind auch UGT1A1, 1A3, 1A8, 1A9, 2B7 und 2B15 und andere in geringerem Maße. Man fand im Folgenden genetische Polymorphismen, die man für die verschiedenen Reaktionen sowie unerwünschten Nebenwirkungen verantwortlich machte[21].

Das zweite Beispiel betrifft die Therapie mit dem Antikoagulanz Warfarin. Es stellte sich heraus, dass Warfarin nicht direkt Substrat der verschiedenen UGT Isoformen ist, sondern erst die Metaboliten, die durch den Abbau durch P450 von Warfarin entstehen. Beteiligt bei der Metabolisierung sind die Enzyme UGT1A1, 1A3, 1A10, 1A8, 1A9, wobei jedes Enzym ein spezifisches Substrat der verschiedenen Abbauprodukte von Warfarin metabolisiert. Nicht beteiligt sind UGT1A4, 1A6, 1A7 und 2B7[22]. Aufgrund der geringen therapeutischen Breite des Warfarins sind regelmäßige Kontrollen der Blutgerinnungswerte bei den Patienten notwendig. Ist die Dosis zu gering, besteht die Gefahr der Entstehung von Thromben. Bei zu hoher Dosierung kann es zu Blutungen kommen. Das unterschiedliche Ansprechen der Patienten auf Warfarin liegt wiederum an dem Auftreten von Polymorphismen, wobei festgestellt wurde, dass z. B. Afroamerikaner anders reagieren als aus Asien stammende Amerikaner.

Es gibt einige Gründe dafür, dass diese Enzyme im Vergleich zu den CYPs bisweilen vernachlässigt wurden. Zum einen die Komplexizität des Glucuronidationsprozesses und zum anderen auch die Schwierigkeit analytische Verfahren zu entwickeln, die Glucuronidation zu erfassen[23]. Zum anderen war der Fokus des Abbaus pharmakologischer Substanzen lange Zeit auf die CYP- Enzyme gerichtet. Welche Rolle diese Enzyme im Körper einnehmen lässt sich anhand verschiedener Krankheiten, die mit einer Störung in diesem Bereich in Zusammenhang stehen, verdeutlichen.

Das vorhin erwähnte Crigler-Naijar Syndrom existiert in zwei Formen. Bei Typ 1 tritt in den ersten Lebenstagen eine Gelbsucht auf, die persistiert. Der Serumbilirubinspiegel ist stark erhöht. Die Krankheit wird autosomal rezessiv vererbt. Im hepatischen Gewebe lässt sich keine Expression des UGT1A1 Enzyms nachweisen. Außerdem spricht der Organismus der von diesem Polymorphismus Betroffenen nicht auf eine Behandlung mit Phenobarbital an, welches als potenter Enzyminduktor der Enzyme der Glukuronidierung gilt. Die meisten Patienten des Typ 1A haben eine Mutation in einem Exon 2-5 des UGT1A1 Enzyms (in der

mRNA erscheinende, und damit exprimierte Gensequenzen) und zusätzlich Schwierigkeiten beim Metabolismus bestimmter anderer Stoffe. Wenige Patienten des Typs 1B haben Mutationen, die auf ein Bilirubin spezifisches A1 Exon beschränkt sind. Hier begrenzt sich der Defekt hauptsächlich auf den Bilirubinstoffwechsel. Der Typ 2 wird autosomal dominant vererbt. Im Gegensatz zum Typ 1 lässt sich hier eine verminderte Expression des UGT1A1 nachweisen, sodass diese Patienten auf eine Behandlung mit dem Enzyminduktor Phenobarbital ansprechen, was die Enzyme der Glukuronidierung induziert [24].

Eine weitere Erkrankung, die mit UGT zusammenhängt, ist das bereits vorher erwähnte Gilbert-Meulengracht-Syndrom. Bei dieser autosomal dominant vererbten Erkrankung, die etwa 5% der Bevölkerung betrifft, liegt eine Störung im Bilirubintransport- und abbau in der Leber vor. Die Aktivität der UGTs ist auf etwa 30% im Vergleich zum Gesunden herabgesetzt, was die Bildung von konjugiertem Bilirubin erschwert. Es resultiert ein erhöhter Bilirubin-Serumspiegel[25].

Sehr gut untersucht ist auch der Zusammenhang zwischen Irinotectan, einem Zytostatikum aus der Gruppe der Topoisomerasehemmer zur Behandlung bestimmter Krebserkrankungen, und UGT1A1. UGT1A1 ist das Hauptenzym bei der Inaktivierung von SN-38, dem aktiven Metabolit von Irinotecan. Verschiedene Polymorphismen dieses Enzyms sind verantwortlich für die individuell unterschiedliche Toxizität von Irinotecan[26]. Die Polymorphismen die auftreten betreffen das UGT1A1 Enzym, was dafür verantwortlich ist, dass der aktive Metabolit SN-28 in sein beta- Glucuronid konjugiert, und somit vom Körper ausscheidbar wird. Patienten mit einer verminderten UGT1A1 Enzymaktivität haben somit, ähnlich wie beim Krankheitsbild des Morbus Meulengracht ein erhöhtes Risiko einer Irinotecan - Toxizität.

# 2. Material und Methode

Die alphabetisch geordnete Tabelle beinhaltet 504 Substanzen, die fast sämtlich pharmakologische Substanzen sind. Es befinden sich auch andere Substanzen wie Estradiol oder Ethanol in der Liste. Auch körpereigene Substrate sind vertreten, z. B. Insulin. Die einzelnen Substanzen wurden in die Suchmaschine der Seite http://www.pubmed.com eingegeben. PUBMED bietet eine Vielzahl an Recherchemöglichkeiten aus dem medizinischen Bereich. Durch den Zugang zu den meisten medizinischen Fachzeitschriften und weltweiten Datenbanken bietet es ein hilfreiches Forum für Mediziner, Studenten und Doktoranden. Die Literatursuche wurde durch diese Datenbank deutlich vereinfacht und auf relevante Links wird ebenfalls verwiesen. Für die Erstellung der Tabelle wurden verschiedene Systeme ausprobiert, um relevante Artikel zu finden. Diese sollten möglichst sowohl die jeweilige Substanz, als auch deren Zusammenhang mit UGT-Enzymen beinhalten. Bei der Eingabe der Substanzen zusammen mit dem Begriff „UGT“ in die Suchmaschine fanden wir zunächst keine brauchbaren Ergebnisse, da diese Abkürzung in den Artikeln nicht verwendet wurde. Es wurden im Folgenden die jeweiligen Substanzen mit dem Anhang „and glucuronosyltransferase“ eingegeben, sodass jeder Artikel der beide Begriffe beinhaltet erscheint. Die Anzahl der Treffer pro Substanz war sehr unterschiedlich, von 0 bis 457. Zu den meisten der untersuchten Substanzen ergab sich eine Trefferanzahl von unter 100. Aufgrund dieser enormen Diskrepanzen wurde ein System eingeführt um die Trefferzahl zu selektieren. Die pubmed Recherche bietet dem Suchenden Möglichkeiten, die Suche auf bestimmte Weise zu selektieren. Beispielsweise kann man durch Limitierungen (limits) die Suche auf Reviews beschränken. Unter der Kategorie „limits“ auf der Internetseite von PUBMED wurde als Limitierung Review-Artikel eingegeben, um zunächst Arbeiten zu erhalten, welche einen guten Überblick über die Verstoffwechselung des entsprechenden

Medikamentes über das UGT ergaben. Meist reichte dies jedoch nicht aus um alle relevanten Artikel zu erfassen, sodass im Folgenden zusätzlich die Suche auf alle Arten von Artikeln ausgedehnt, aber auf die letzten 5 Jahre beschränkt wurde. Desweiteren wurden die Artikel nach Studien selektiert, die sich nur mit menschlichem Material beschäftigten, von denen wir möglichst viele in die Tabelle mit aufnehmen konnten, ohne die Tabelle unnötig in die Länge zu ziehen. Zusammen mit der Limitierung auf Studien, die sich auf Versuche an menschlichem Material beschränken (mit der Limitierung „humans“, für menschliches Material), wurden so gezielt die für die Tabelle brauchbarsten und gleichzeitig aktuellsten Artikel herausgefiltert.

Methodische Probleme lagen beispielsweise bei der Auswahl der für die Tabelle relevanten Artikel, da sich der Inhalt der Ergebnisse bei den verschiedenen Versuchen oft überschnitten hatte. Somit wurden die Literaturzitate dahingehend beschränkt, dass einerseits nicht wichtige Informationen verloren gingen, andererseits nicht allzu viele inhaltlich identische Ergebnisse miteingebracht wurden. Die Arbeit ist somit limitiert worden auf die zeitlich aktuellsten Artikel der letzten 5 Jahre, sowie auf die Artikel, die sich mit den Studien an menschlichem Material beschäftigen, um eine möglichst hohe klinische Relevanz zu erzeugen und die Übersichtlichkeit zu wahren. Insgesamt sechsmal ergab sich der Fall, dass in den Artikeln selber beschrieben war, dass ein Zusammenhang zwischen dem Substrat und UGT Enzymen noch nicht sicher erwiesen ist. Dieser Umstand wurde mit der Abkürzung „U“ für unsicher gekennzeichnet.

Ein weiteres Problem ergab sich dadurch, dass sich die Anzahl der Treffer im Laufe der Zeit der Recherchen geändert hat, bzw. weitere Artikel als Treffer bei PUBMED erschienen. Bei der Einfügung der Artikel als Endnoten wurde, wenn es aus dem Text hervorging, in Klammern das entsprechende UGT-Enzym miteingefügt. Desweiteren wurde vermerkt, welche Substanzen als Inhibitoren, und welche als Induktoren fungieren. Mit der Abkürzung „WW“ wurden zusätzlich relevante Wechselwirkungen mit der jeweiligen Substanz

mitaufgenommen. Es wurde auch vermerkt, ob sich die Studie mit lebendem Material beschäftigt, also „in vivo“, oder mit Zellkulturen gearbeitet wurde „in vitro“, bzw, „cell lines“. Für Studien mit Tierversuchen wurde die Abkürzung „t“ eingeführt. So bedeutet beispielsweise die Anmerkung (UGT1A4, in vitro, induction, WW: Phenobarbital) dass die Substanz XY über das UGT-Enzym UGT1A4 metabolisiert wird. Die Studie beschäftigte sich mit Zellkulturen. Diese Substanz bewirkt eine Induktion des Enzyms, und bei der Metabolisierung ergibt sich eine Wechselwirkung mit dem Substrat Phenobarbital. Die Vorgehensweise bei der Erstellung der Tabelle verlief wie folgt an zwei Beispielen:

Phenobarbital, ein Arzneistoff der Gruppe der Barbiturate, ergab zusammen mit der Kombination „and glucuronosyltrandferase“ in der Suchmaschine der Seite www.pubmed.com 457 Treffer. Um nun nicht alle 457 Artikel bearbeiten zu müssen, wurde die Limitierung auf die Artikel der letzten 5 Jahre sowie auf die Artikel die sich mit Studien an menschlichem Material beschäftigen gesetzt. Dies ist insofern sinnvoll, da unter den 457 ursprünglichen Treffen mehr als 300 Artikel älter als fünf Jahre waren und somit davon ausgegangen wurde, dass die Informationen teilweise redundant sind und die Information neuer Artikel für die Beurteilung klinischer Relevanz entscheidend. Die Suche mit den gewählten Limitierungen ergab nun 28 Treffer, wovon nach genauer Durchsicht 12 Artikel als relevant in die Tabelle aufgenommen wurden. Bei anderen Substraten jedoch ergab sich, dass die Suche nur drei Treffer ergab, wie bei dem Arzneistoff Miconazol, aus der Gruppe der Imidaziole, zur Behandlung von Pilzerkrankungen. In diesem Fall wurden alle 3 Treffer in die Tabelle mitaufgenommen, um keine Information, obwohl möglicherweise unbedeutend zu vernachlässigen.

# 3. Ergebnisse

## 3.1. Interaktionstabelle

| Substanz | Treffer | Ergebnis |
|---|---|---|
| Acebutolol | 0 | |
| Acenocoumarol | 0 | |
| Acetazolamid | 0 | |
| Acetylsalicylsäure | 0 | |
| Äthanol | 0 | |
| Äthinylöstradiol | 24 | X[1 2 3 4 5 6 7 8 9 10 11] |
| Äthylöstradiol | 0 | |
| Äthylmorphin | 33 | kein Substrat |
| Ätonorgestrel | 0 | |
| Ajmalin | 0 | |
| Albendazol | 1 | X[1] |
| Albuterol (Salbutamol) | 4 | X[1 2] |
| Aldosteron | 6 | X[1 2 3] |
| Alfentanil | 1 | kein Substrat |
| Alkohol | 288 (14r, 44y, h) | X[1] |
| Almotriptan | 0 | |
| Alprazolam | 1 | kein Substrat |
| Alprenolol | 0 | |
| Aminogluthethimid | 0 | |
| Aminophyllin | 0 | |
| Amiodaron | 2 | X[1] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Amisulprid | 1 | U[1] |
| Amitryptilin | 0 | |
| Amlodipin | 0 | |
| Amobarbital | 1 | X[1] |
| Amphetamin | 1 | kein Substrat |
| Amprenavir | 0 | |
| Amrinon | 0 | |
| Anastrozol | 1 | kein Substrat |
| Androsteron | 118 (4r, 13y, h) | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39] |
| Anilin | 103 | kein Substrat |
| Aprindin | 0 | |
| Aripiprazol | 1 | kein Substrat |
| Astemizol | 1 | kein Substrat |
| Atorvastatin | 5 | X[1 2 3] |
| Azapropazon | 0 | |
| Azelastin | 0 | |
| Azithromycin | 1 | kein Substrat |
| Beclometason | 1 | X[1] |
| Bezafibrat | 7 | X[1 2 3 4 5 6] |
| Bepridil | 0 | |
| Betamethason | 1 | kein Substrat |
| Betaxolol | 0 | |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Bexarolen | 0 | |
| Biperiden | 0 | |
| Bisoprolol | 0 | |
| Bopindolol | 0 | |
| Bosentan | 0 | |
| Brinzolamid | 0 | |
| Brokkoli (Sulforaphan) | 10 | X[1 2 3 4 5] |
| Bromazepam | 0 | |
| Bromocriptin | 0 | |
| Budesonid | 1 | kein Substrat |
| Bufurolol | 3 | kein Substrat |
| Bupivacain | 0 | |
| Buprenorphin | 15 | X[1 2 3 4 5 6 7 8 9 10 11] |
| Bupropion | 1 | kein Substrat |
| Buspiron | 1 | kein Substrat |
| Busulfan | 0 | |
| Cafergot | 0 | |
| Calcitriol (Vit. D) | 6 | X[1 2 3 4] |
| Candesartan | 0 | |
| Capsaicin | 2 | X[1 2] |
| Captopril | 0 | |
| Carbamazepin | 19 | X[1 2 3 4 5 6 7 8 9 10 11] |
| Carisoprodol | 0 | |
| Carmustin | 2 | kein Substrat |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Carteolol | 1 | kein Substrat |
| Carvedilol | 8 | X[1 2 3 4 5 6 7 8] |
| Celecoxib | 0 | |
| Cerivastatin | 4 | X[1] |
| Cetirizin | 1 | X[1] |
| Chinidin | 1 | kein Substrat |
| Chinin | 0 | |
| Chlorambucil | 0 | |
| Chloramphenicol | 64 | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23] |
| Chlordiazepoxid | 0 | |
| Chloroquin | 4 | X[1 2] |
| Chlorpheniramin | 2 | X[1] |
| Chlorpromazin | 13 | X[1 2 3 4 5] |
| Chlorpropamid | 0 | |
| Chlorzoxazon | 5 | kein Substrat |
| Cholecalciferol | 6 | X[1 2 3] |
| Ciclosporin A | 11 | X[1 2] |
| Cimetidin | 12 | X[1] |
| Cinnarizin | 0 | |
| Ciprofloxacin | 0 | |
| Cisaprid | 2 | X[1] |
| Citalopram | 1 | U |
| Clarithromycin | 1 | kein Substrat |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Clemastin | 0 | |
| Clobazam | 1 | X[1] |
| Clofibrat | 60 | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24] |
| Clomipramin | 4 | X[1 2] |
| Clonazepam | 3 | X[1] |
| Clonidin | 0 | |
| Clopidogrel | 0 | |
| Clorazepat | 0 | |
| Clotrimazol | 4 | X[1 2 3 4] |
| Clozapin | 5 | X[1 2 3] |
| Cocain | 2 | X[1] |
| Codein | 26 | X[1 2 3 4 5 6 7] |
| Coffein | 0 | |
| Colchicin | 3 | kein Substrat |
| Cortisol (Hydrocortison) | 27 | X[1 2 3 4] |
| Cortison | 1 | kein Substrat |
| Cumarin | 36 | X[1 2 3 4 5 6 7] |
| Cyclobenzaprin | 1 | kein Substrat |
| Cyclophosphamid | 7 | X[1] |
| Cyclosporin A | 14 | X[1 2 3 4] |
| Dacarbazin | 1 | kein Substrat |
| Danazol | 0 | |
| Dantrolen | 1 | X[1] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Dapson | 0 | |
| Debrisoquin | 4 | X[1] |
| Delaviridin | 0 | |
| Desipramin | 1 | kein Substrat |
| Desogestrel | 0 | |
| Dexamethason | 66 (12y,h) | X[1 2 3 4 5 6 7 8] |
| Dexfenfluramin | 0 | |
| Dextromethorphan | 8 | kein Substrat |
| Diabetes mellitus | 27 | X[1 2 3 4 5 6 7 8] |
| Diazepam | 12 | X[1 2 3] |
| Diclofenac | 33 | X[1 2 3 4 5 6 7 8 9 10 11 12] |
| Dicloxacillin | 0 | |
| Dicumarol | 4 | X[1] |
| Didanosin | 2 | kein Substrat |
| Diethyldithiocarbamat | 8 | kein Substrat |
| Digitoxin | 16 | X[1] |
| Digoxin | 4 | X[1] |
| Dihydrocodein | 1 | X[1] |
| Dihydroergotamin | 0 | |
| Diltiazem | 2 | kein Substrat |
| Dimethylsulfoxid | 14 | X[1 2] |
| Diphenhydramin | 4 | X[1 2] |
| Disopyramid | 0 | |
| Disulfiram | 7 | X[1 2] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Dithiocarbamat | 3 | kein Substrat |
| Dofetil | 0 | |
| Dolasetron | 0 | |
| Domperidon | 0 | |
| Donepezil | 0 | |
| Dorzolamid | 0 | |
| Doxepin | 1 | kein Substrat |
| Doxorubicin | 9 | kein Substrat |
| Doxycyclin | 1 | kein Substrat |
| Drospirenon | 0 | |
| Duloxetin | 0 | |
| Econazol | 0 | |
| “Ecstasy” (MDMA) | 0 | |
| Efavirenz | 2 | X[1] |
| Eletriptan | 0 | |
| Enalapril | 0 | |
| Encainid | 0 | |
| Enfluran | 2 | X[1 2] |
| Enoxacin | 1 | kein Substrat |
| Entacapon | 12 | X[1 2 3 4 5 6] |
| Eplerenon | 0 | |
| Eprosartan | 0 | |
| Ergotamin | 0 | |
| Erythromycin | 17 | X[1] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Escitalopram | 1 | kein Substrat |
| Esomeprazol | 5 | kein Substrat |
| Estradiol | 168 (48y,h,5r) | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15] |
| Ethinylestradiol | 30 | X[1 2 3 4 5 6 7 8 9] |
| Ethosuximid | 3 | kein Substrat |
| Ethylestradiol | 0 | |
| Ethylmorphin | 33 | kein Substrat |
| Etonorgestrel | 0 | |
| Etoposid | 4 | X[1 2 3] |
| Etoricoxib | 0 | |
| Exemestan | 0 | |
| Fasten | 0 | |
| Felbamat | 5 | kein Substrat |
| Felodipin | 0 | |
| Fenofibrat | 10 | X[1 2 3 4] |
| Fentanyl | 2 | X[1] |
| Fexofenadin | 0 | |
| Finasterid | 1 | kein Substrat |
| Flavonoide (Grapefruitsaft) | 170 (6r, 42y, h) | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16] |
| Flecainid | 0 | |
| Fluconazol | 10 | X[1 2 3 4 5 6] |
| Flunarizin | 0 | |
| Flunitrazepam | 6 | X[1 2 3 4] |
| Fluoruracil | 21 | X[1] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Fluoxetin | 0 | |
| Flupentixol | 0 | |
| Fluphenazin | 3 | kein Substrat |
| Flurazepam | 0 | |
| Flurbiprofen | 11 | X[1 2 3 4 5 6 7 8 9] |
| Flutamid | 2 | X[1 2] |
| Fluticason | 1 | kein Substrat |
| Fluvastatin | 2 | kein Substrat |
| Fluvestrant | 2 | X[1] |
| Fluvoxamin | 1 | kein Substrat |
| Formoterol | 1 | kein Substrat |
| Fosphenytoin | 0 | |
| Furafylline | 0 | |
| Galantamin | 0 | |
| Gemfibrozil | 7 | X[1 2 3 4 5] |
| Gestoden | 0 | |
| Gleevec | 1 | X[1] |
| Glibenclamid | 0 | |
| Glimepirid | 0 | |
| Glipizid | 1 | kein Substrat |
| Glyburid | 0 | |
| Granisetron | 0 | |
| Griseofulvin | 1 | X[1] |
| Halofantrin | 0 | |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Haloperidol | 4 | X[1 2 3] |
| Halothan | 4 | X[1 2] |
| Hexobarbital | 15 | kein Substrat |
| Hydralazin | 4 | kein Substrat |
| Hydrocodon | 1 | kein Substrat |
| Hydroxyzin | 1 | kein Substrat |
| Hyperforin (Johanniskraut) | 0 | |
| Ibuprofen | 20 | X[1 2 3 4 5 6 7 8 9 10] |
| Ifosfamid | 1 | kein Substrat |
| Imatinib | 1 | X[1] |
| Imipramin | 27 | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15] |
| Imiquimod | 0 | |
| Indinavir | 5 | X[1 2 3 4] |
| Indomethacin | 18 | X[1 2 3 4 5 6 7 8] |
| Indoramin | 0 | |
| Insulin | 36 | X[1 2 3] |
| Interferon | 21 | X[1 2] |
| Irbesartan | 1 | kein Substrat |
| Irinotecan | 159 (48r, 113y, h) | X[1 2 3 4 5 6 7 8 9 10 11 12] |
| Isofluran | 1 | X[1] |
| Isoniazid | 12 | X[1] |
| Isosorbiddinitrat (ISDN) | 0 | |
| Isosorbidmononitrat (ISMN) | 0 | |
| Isradipin | 0 | |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Itraconazol | 3 | kein Substrat |
| Ivermectin | 0 | |
| Johanniskraut | 0 | |
| Josamycin | 0 | |
| Ketamin | 3 | X[1] |
| Ketoconazol | 13 | X[1 2 3 4] |
| Ketoprofen | 19 | X[1 2 3 4 5 6 7 8 9 10 11] |
| LAAM (Levacetylmethadol) | 0 | |
| Labetalol | 1 | X[1] |
| Lamivudin | 1 | kein Substrat |
| Lamotrigin | 21 | X[1 2 3 4] |
| Lansoprazol | 1 | X[1] |
| Leflunomid | 1 | kein Substrat |
| Lercanidipin | 0 | |
| Letrozol | 1 | kein Substrat |
| Levofloxacin | 3 | X[1] |
| Levomepromazin | 0 | |
| Levonorgestrel | 2 | kein Substrat |
| Levothyroxin-Natrium | 121 (2r, 8y, h) | X[1 2 3 4 5 6 7 8 9 10 11 12] |
| Lidocain | 2 | kein Substrat |
| Lomefloxacin | 0 | |
| Lomustin | 1 | kein Substrat |
| Loperamid | 2 | kein Substrat |
| Lopinavir | 4 | X[1] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Loratadin | 2 | X[1 2] |
| Losartan | 1 | kein Substrat |
| Lovastatin | 7 | kein Substrat |
| Lumiracoxib | 0 | |
| Maprotilin | 0 | |
| MDMA (“Ecstasy”) | 0 | |
| Medroxyprogesteron | 2 | X[1] |
| Mefenaminsäure | 0 | |
| Mefloquin | 0 | |
| Melatonin | 0 | |
| Meloxicam | 0 | |
| Melperon | 0 | |
| Mephenytoin | 13 | kein Substrat |
| Mestranol | 2 | kein Substrat |
| Metformin | 0 | |
| Methamphetamin | 1 | kein Substrat |
| Methadon | 6 | X[1 2 3 4] |
| Methosuximid | 0 | |
| Methoxsalen | 1 | kein Substrat |
| Methoxyamphetamin | 0 | |
| Methoxyfluran | 1 | X[1] |
| Methylphenidat | 0 | |
| Methylphenobarbital | 1 | X[1] |
| Methylprednisolon | 1 | X[1] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Methysergid | 0 | |
| Metoclopramid | 0 | |
| Metoprolol | 1 | kein Substrat |
| Metronidazol | 0 | |
| Mexiletin | 0 | |
| Mianserin | 0 | |
| Mibefradil | 0 | |
| Miconazol | 3 | X[1 2 3] |
| Midazolam | 11 | X[1 2 3] |
| Mifepriston | 3 | kein Substrat |
| Minaprin | 1 | kein Substrat |
| Mirtazapin | 0 | |
| Mitoxantron | 4 | X[1 2] |
| Moclobemid | 0 | |
| Modafinil | 0 | |
| Mometasonfuroat | 0 | |
| Montelukast | 0 | |
| Moricizin | 0 | |
| Morphin | 235(8r, 28y, h) | X[1 2 3 4 5 6 7 8 9 10 11 12] |
| Nafcillin | 0 | |
| Nalidixinsäure | 0 | |
| Naphtoflavon | 90(1r, 9y, h) | X[1 2 3 4 5 6] |
| Naproxen | 24 | X[1 2 3 4 5 6 7 8 9 10 11 12 13] |
| Naringenin (Grapefruit) | 9 | X[1 2 3 4 5 6] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Nateglinid | 0 | |
| Nefazodon | 1 | kein Substrat |
| Nelfinavir | 3 | X[1 2] |
| Nevirapin | 0 | |
| Nicardipin | 2 | X[1] |
| Nikotin | 15 | X[1 2 3 4 5 6 7 8] |
| Nifedipin | 7 | kein Substrat |
| Nilutamid | 0 | |
| Nimodipin | 0 | |
| Niniodipin | 0 | |
| Nisoldipin | 0 | |
| Nitrazepam | 2 | kein Substrat |
| Nitrendipin | 0 | |
| Nordazepam | 0 | |
| Norethindron | 3 | kein Substrat |
| Norethisteron | 3 | kein Substrat |
| Norfloxacin | 0 | |
| Norfluoxetin | 0 | |
| Nortriptylin | 2 | kein Substrat |
| N-Propylajmalin | 0 | |
| Odansetron | 1 | kein Substrat |
| Ofloxacin | 2 | kein Substrat |
| Olanzapin | 6 | X[1 2 3] |
| Omeprazol | 8 | |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Ondansetron | 1 | X[1] |
| Orphenadrin | 0 | |
| Oxazepam | 22 | X[1 2 3 4 5 6 7 8 9 10] |
| Oxcarbazepin | 5 | kein Substrat |
| Oxprenolol | 0 | |
| Oxybutynin | 0 | |
| Oxycodon | 1 | kein Substrat |
| Paclitaxel = Taxol | 3 | kein Substrat |
| Paliperidon | 0 | |
| Pantoprazol | 1 | X[1] |
| Paracetamol | 132(4r, 23h,y) | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14] |
| Parecoxib | 0 | |
| Paroxetin | 1 | kein Substrat |
| Penbutolol | 0 | |
| Pentamidin | 0 | |
| Pentobarbital | 9 | X[1 2 3 4] |
| Pentoxifyllin | 0 | |
| Perazin | 0 | |
| Pergolid | 0 | |
| Perhexilin | 0 | |
| Perphenazin | 1 | X[1] |
| Phenacetin | 5 | kein Substrat |
| Phenformin | 0 | |
| Phenobarbital | 457(28r, 28y,h) | X[1 2 3 4 5 6 7 8 9 10 11 12] |

| Substanz | Treffer | Ergebnis |
|---|---|---|
| Phenprocoumon | 0 | |
| Phenylbutazon | 10 | X[1 2 3 4 5 6] |
| Phenytoin | 28 | X[1 2 3 4 5 6 7 8] |
| Picrolimus | 0 | |
| Pilocarpin | 1 | kein Substrat |
| Pimozid | 1 | kein Substrat |
| Pindolol | 0 | |
| Pioglitazone | 0 | |
| Piroxicam | 1 | kein Substrat |
| Prajmalin | 0 | |
| Pramipexol | 0 | |
| Praziquantel | 2 | kein Substrat |
| Pravastatin | 2 | kein Substrat |
| Prazepam | 0 | |
| Prazosin | 2 | kein Substrat |
| Prednisolon | 2 | kein Substrat |
| Prednison | 1 | kein Substrat |
| Pregabalin | 3 | kein Substrat |
| Primaquin | 0 | |
| Primidon | 4 | X[1 2 3] |
| Probenecid | 16 | X[1 2 3 4 5 6 7 8 9 10] |
| Procainamid | 0 | |
| Progesteron | 33 | X[1 2 3 4 5 6] |
| Proguanil | 0 | |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Promethazin | 5 | X[1 2] |
| Propafenon | 4 | X[1 2 3] |
| Propofol | 42 | X[1 2 3 4 5 6 7 8 9 10 11 12 13 14 15] |
| Propranolol | 6 | X[1 2] |
| Pyrimethamin | 0 | |
| Quanoxan | 0 | |
| Quetiapin | 2 | X[1] |
| Quinidin | 5 | X[1] |
| Quinin | 5 | X[1 2] |
| Quinupristin | 0 | |
| Rabeprazol | 0 | |
| Ranitidin | 5 | X[1 2 3] |
| Rauchen (smoke) | 28 | X[1 2 3 4 5 6 7 8] |
| Reboxetin | 0 | |
| Repaglinide | 0 | |
| Retigabin | 3 | X[1 2 3] |
| Rifabutin | 2 | X[1] |
| Rifampicin | 38 | X[1 2 3 4 5 6 7 8 9 10 11] |
| Rifapentin | 0 | |
| Riluzol | 2 | X[1 2] |
| Risperidon | 3 | kein Substrat |
| Ritonavir | 11 | X[1 2] |
| Rofecoxib | 1 | X[1] |
| Ropinirol | 0 | |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Ropivacain | 0 | |
| Rosiglitazon | 0 | |
| Roxithromycin | 0 | |
| R-Warfarin | 1 | kein Substrat |
| Salmeterol | 1 | kein Substrat |
| Saquinavir | 4 | X[1 2] |
| Secobarbital | 0 | |
| Selegelin | 0 | |
| Sertindol | 0 | |
| Sertralin | 1 | X[1] |
| Sevofluran | 2 | kein Substrat |
| Sibutramin | 0 | |
| Sildenafil | 0 | |
| Simvastatin | 6 | X[1 2] |
| Sirolimus | 3 | X[1] |
| S-Mephenytoin | 10 | kein Substrat |
| Sparfloxacin | 0 | |
| Spartein | 3 | kein Substrat |
| Spiramycin | 1 | kein Substrat |
| St.-John’s wort (Johanniskraut) | 5 | kein Substrat |
| Stavudin | 0 | |
| Sufentanil | 0 | |
| Sulfadiazin | 2 | kein Substrat |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Sulfafurozol | 0 | |
| Sulfamethazin | 3 | kein Substrat |
| Sulfamethoxazol | 1 | kein Substrat |
| Sulfaphenazol | 4 | kein Substrat |
| Sulfinpyrazol | 0 | |
| Sulfinpyrazon | 4 | X[1 2 3] |
| Suprofen | 0 | |
| S-Warfarin | 1 | kein Substrat |
| Tabak | 0 | |
| Tacrin | 0 | |
| Tacrolimus | 16 | X[1 2 3] |
| Tamoxifen | 19 | X[1 2 3 4 5 6 7 8 9] |
| Tamsulosin | 1 | kein Substrat |
| Taxol = Paclitaxel | 3 | kein Substrat |
| Teerstoffe (Tabakrauch) | 0 | |
| Telithromycin | 0 | |
| Telmisartan | 0 | |
| Temazepam | 2 | kein Substrat |
| Teniposid | 0 | |
| Tenofovir | 1 | kein Substrat |
| Tenoxicam | 1 | kein Substrat |
| Terbinafin | 0 | |
| Terfenadin | 3 | kein Substrat |
| Testosteron | 265 (1r, 21y,h) | X[1 2 3 4 5 6 7 8] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Tetracyclin | 2 | kein Substrat |
| Theophyllin | 6 | kein Substrat |
| Thiamazol | 4 | kein Substrat |
| Thioridazin | 0 | |
| Thiotepa | 0 | |
| Thiothixen | 0 | |
| Tiabendazol | 0 | |
| Tiagabin | 5 | kein Substrat |
| Ticlopidin | 1 | kein Substrat |
| Timolol | 0 | |
| Tizanidin | 0 | |
| Tocainid | 1 | kein Substrat |
| Tolbutamid | 7 | kein Substrat |
| Tolcapon | 7 | X[1 2 3 4] |
| Tolterodin | 0 | |
| Topiramat | 7 | U[1 2] |
| Torasemid | 0 | |
| Toremifen | 0 | |
| Tramadol | 5 | X[1 2 3] |
| Tranylcypromin | 0 | |
| Trazodon | 0 | |
| Tretinoin<br>= Vitamin A-Säure | 21 | X[1 2 3 4 5 6 7 8 9 10] |
| Triamcinolon | 2 | X[1] |

| **Substanz** | **Treffer** | **Ergebnis** |
|---|---|---|
| Triazolam | 0 | |
| Trifluperazin | 15 | X[1 2 3 4 5 6 7] |
| Trimethoprim | 1 | kein Substrat |
| Trimipramin | 0 | |
| Troglitazon | 7 | X[1 2 3 4 5] |
| Troleandomycin | 5 | X[1] |
| Tropisetron | 0 | |
| Urapidil | 0 | |
| Valdecoxib | 0 | |
| Valproinsäure | 0 | |
| Valsartan | 0 | |
| Vardenafil | 0 | |
| Venlafaxin | 1 | kein Substrat |
| Verapamil | 2 | kein Substrat |
| Vinblastin | 3 | kein Substrat |
| Vincristin | 1 | kein Substrat |
| Vindesin | 1 | kein Substrat |
| Vinorelbin | 2 | X[1] |
| Voriconazol | 0 | |
| Warfarin | 7 | X[1] |
| Yohimbin | 0 | |
| Zacitabin | 0 | |
| Zafirlukast | 0 | |
| Zaleplon | 0 | |

| Substanz | Treffer | Ergebnis |
|---|---|---|
| Zidovudin | 43 | X[1 2 3 4 5 6 7 8 9 10 11 12] |
| Zileuton | 2 | kein Substrat |
| Ziprasidon | 1 | U[1] |
| Zolmitriptan | 0 | |
| Zolpidem | 0 | |
| Zonisamid | 3 | U[1 2] |
| Zopiclon | 0 | |
| Zotepin | 0 | |
| Zuclopenthixol | 1 | U[1] |

# Legende

X: Substrat

U: unsichere Datenlage

r: Limitierung auf Reviews

y: Limitierung auf die letzten 5 Jahre

h: Limitierung auf Studien mit menschlichem Material

Die Tabelle beinhaltet 504 Substanzen. Die Anzahl der Treffer geht von 0 bis 457. Folgende Substanzen ergaben mehr als 100 Treffer: Alkohol (288), Androsteron (118), Anilin (103), Estradiol (168), Flavonoide (170), Irinotecan (159), Levothyroxin-Natrium (121), Morphin (235), Paracetamol (132), Phenobarbital (457) und Testosteron (265).

Folgende Substanzen ergaben zwischen 50 und 100 Treffer: Chloramphenicol, Clofibrat, Dexamethason und Naphtoflavon.

Desweiteren ergaben 220 Substanzen zwischen 0 und 10 Treffer, 220 Substanzen 10 bis 50 Treffer und 49 Substanzen 50 bis 100.

Bei 42 Substanzen wurde eine Induktion eines oder mehrerer UGT-Enzyme festgestellt, während bei 52 Substanzen eine Inhibition festgestellt wurde.

Bei 82 Substanzen bezogen sich die Studien ausschließlich auf Versuchen an Tieren, bzw. in vitro oder in cell lines.

Folgende UGT- Isoenzyme werden in der Literatur am häufigsten zitiert: UGT 1A1, 1A3, 1A4, 1A6, 1A8, 1A10, sowie 2B7, 2B9, 2B15 und 2B17, wobei mit Abstand die UGT1A1 und 2B7 an erster Stelle stehen. Eher seltener kommen die UGT2B33 sowie 1A7 vor. Noch seltener beispielsweise die UGT2B1 und 2B12.

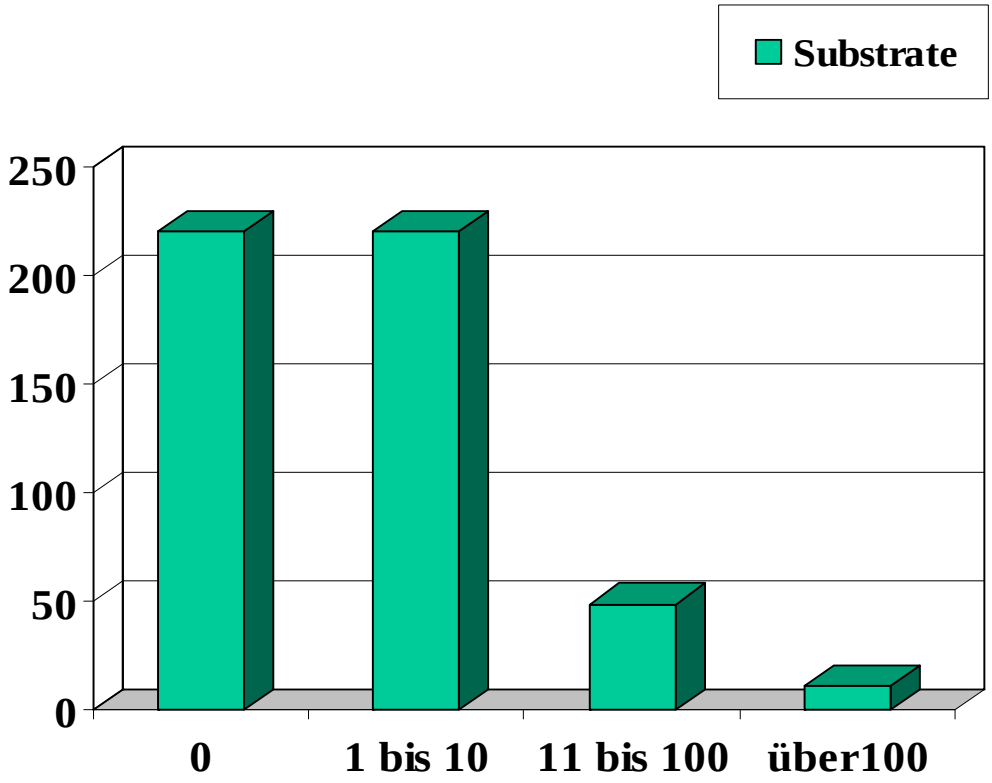
# 4. Diskussion

Insgesamt lässt sich feststellen, dass nur vergleichsweise wenige Substanzen sehr gut untersucht sind mit über 100 Publikationen, wobei dies kein Gütekriterium für die Qualität der Untersuchungen darstellt. Bei vielen Substanzen gibt es jedoch nur sehr wenige Untersuchungen, vor allem in vitro. Eine differenzierte Beurteilung des Interaktionspotentials in vivo ist dadurch erschwert. Allerdings ist festzustellen, dass die UGT-Enzyme noch nicht sehr lange im Fokus wissenschaftlicher Untersuchungen zum Interaktionspotential sind. Im Gegenteil, im klinischen Alltag finden zumeist allenfalls Interaktionstabellen zu den Cytochrom-Enzymen praktische Anwendung. Und auch hier sind die Wechselwirkungen im Einzelnen nur schwer vorhersagbar.

Der aktuelle Stand der Anzahl der Studien zu den einzelnen Substanzen weißt auf eine noch sehr heterogene Datenlage hin.

Bei vielen Substanzen, die im klinischen Alltag häufig verordnet werden, liegen bisher keine Untersuchungen zu der Metabolisierung über UGT-Enzyme vor. Die meisten Studien stammen aus den letzten 10 Jahren mit einer aktuell jährlich deutlich ansteigenden Anzahl von Veröffentlichungen. Nur äußerst selten findet man Artikel, die vor 1985 veröffentlicht wurden. Es wurden bei in etwa gleich vielen Substanzen eine potentielle Induktion bzw. Inhibition festgestellt. Ob dies potente – auch im klinischen Alltag – zu relevanten Wechselwirkungen führende Interaktionen sind oder nicht, kann aufgrund der niedrigen Zahl von in-vivo-Studien noch nicht beurteilt werden. Der doch für viele Substanzen hohen Anzahl von Studien steht eine im klinischen Alltag noch eher geringe Aufmerksamkeit für Wechselwirkungen über UGT-Enzyme gegenüber.

# Trefferverteilung




## Legende

x-Achse: Einteilung der Trefferverteilung

y-Achse: Anzahl der Substrate

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(in vivo): Studien über Prozesse, die im lebendigen Organismus ablaufen

(cell lines): Studien mit Zelllinien; Zelllinien sind Zellen einer Gewebeart, die sich im Lauf dieser Zellkultur unbegrenzt fortpflanzen können; es werden sowohl immortalisierte (unsterbliche) Zelllinien als auch primäre Zellen kultiviert (Primärkultur)

(t): Studien mit Versuchen an Material tierischen Ursprungs

(UGTXY): das UGT-Enzym, dem die Substanz als Substrat dient

(WW: XY): eine Wechselwirkung der Substanz mit einer anderen Substanz XY

(polymorphism): von dem UGT-Enzym existieren Polymorphismen

(induktion): die Substanz wirkt auf das UGT-Enzym als Induktor

(inhibition): die Substanz wirkt auf das UGT-Enzym als Inhibitor

**Äthinylöstradiol**

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